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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,046	05/08/2002	Abd. Al-Roof Higazi	143.006	2204

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,046	HIGAZI, ABD. AL-ROOF	
	Examiner	Art Unit	
	Lora E Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 7-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 7, and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 2/14/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In paragraph 0030, line 2, the phrase "has no effect" has been amended to recite "has no **such preventive and/or inhibitory** effect", which dramatically changes the scope and meaning of said phrase.

Applicant is hereby notified that the insertion of new matter into the claims has necessitated the removal of some elements of the enablement rejection over claims 1, 2, 7, and 8. However, removal of new matter will result in the reinstatement of these elements.

Additionally, applicants assert that claims 9 and 10 have been amended and are presently drawn to process claims involving the compositions of product claims 1 and 2, but this is clearly not the case. Claims 1 and 2 recite compositions of a specific hexapeptide and a fibrinolytic agent, while amended claims 9 and 10 are drawn to compositions comprising an antibody and a fibrinolytic agent. Claims 9 and 10 are, therefore, not considered in this Office action as they are drawn to nonelected subject matter (i.e., original Group IV of the restriction requirement mailed 8/27/04). This Office action relates to the matter of claims 1, 2, 7, and 8 **ONLY**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 2, 7, and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are instantly amended to recite the polypeptide EEIIMD in the range of 2μM to 10μM.

Insertion of the limitation "in the range of 2μM to 10μM" has no support in the as-filed specification. The insertion of this limitation is a new concept because it has no literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of the use of EEIIMD in the range of 2μM to 10μM. There is only one exemplified dosage of EEIIMD, i.e. 2μM to rat aortic rings in Example 2. This is not sufficient support for the new genus, the use of EEIIMD in the range of 2μM to 10μM.

Example 2, which is the only example involving the use of EEIIMD, is unclear in terms of dosage. Paragraph 0056 makes assertions regarding the effects of 2 μM and 10μM EEIIMD, but corresponding Figure 2 recites only one concentration of EEIIMD, 10mM. Because of the discrepancy between the text of the specification and the drawings, it is impossible to discern which dosage of EEIIMD was in possession of the inventor at the time the invention was made. The inclusion of 10μM EEIIMD in the claims, therefore, finds insufficient support in the specification to fulfill the written description requirement.

This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept, in this case the range of concentrations of EEIIMD that have a given effect. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the use of EEIIMD in the range of 2μM to 10μM is considered to be the insertion of new matter.

Claims 1, 2, 7, and 8 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In the first Office action on the merits, the examiner pointed out that no specific dosage for the claimed EEIIMD peptide was provided in the claims or specification and that insufficient direction was provided by applicants as to the use of EEIIMD in the claimed method **without causing cranial hemorrhage**. Finally, the examiner maintained that in light of the lack of working embodiments provided in the disclosure and the unpredictability of the art, a person of ordinary skill in the art would not have had a reasonable expectation of success in using the claimed invention at the time it was made.

In response, applicants have amended claims 1 and 7 to recite specific amounts of EEIIMD. Applicants have also asserted that methods of administration and optimizing the same are well known in the art and that the lack of specific methods in the disclosure do not present an enablement problem. Applicants also assert that the combination of scuPA and EEIIMD is exemplified in Figure 1A of the original disclosure.

These arguments are not found persuasive because while applicants have provided specific dosages of the EEIIMD peptide in the claims, these dosages appear to be derived from experiments that do not relate directly to the matter of claims 1 and 7. The working examples are limited to investigating the effects of TNK-tPA on PE-induced contraction of rat aortic rings (Example 1), investigating the effects of PAI-1 and the EEIIMD on TNK-tPA action (Example 2), and investigating the effects of antibodies on TNK-tPA action (Example 3). Applicant's assertion that Figure 1A exemplifies the combination of scuPA and EEIIMD is incorrect, as the brief description of this figure in paragraph 0015 characterizes it as "a diagram describing the results of experiments on the effect of tPA on PE-induced contraction of isolated rat aorta rings", and Figure 1A itself does not recite EEIIMD or any peptide.

In fact, Figure 2 is the only figure that contains any experimental data concerning the effects of EEIIMD, but this figure also fails to support applicant's arguments because it describes co-administration of EEIIMD with either tPA or TNK-tPA, **but not scuPA**, to rat aortic rings. Figure 2 indicates that EEIIMD has a moderate effect on the activity of TNK-tPA and no effect on tPA, but it does not give any information as to the effects of EEIIMD on the elected species, scUPA. Additionally, the effect of any composition on the model system of Example 2 alone (phenylephrine-induced constriction of rat aortic rings) is insufficient to support a claim for treating "a subject" without inducing "cranial hemorrhage". No experiments were conducted on living subjects with heads, so no tests could be performed to assert the presence or absence of cranial hemorrhage during any

treatment. Applicant's assertion that 2-10μM EEIIMD would enhance fibrinolytic activity of scuPA without inducing cranial hemorrhage is unsupported by the disclosure.

The examiner maintains her assertion that the guidance provided by applicants in the specification with regard to dosage of EEIIMD for enhancing the fibrinolytic activity of scuPA (or, indeed, any fibrinolytic agent) **without inducing cranial hemorrhage** (or, indeed, hemorrhage of any kind) in a living subject is insufficient. Although the specification discloses methods of administration of EEIIMD *in vitro*, there are no data on the effectiveness of EEIIMD used in a therapeutic treatment of a particular disease.

Therefore, taking into account the nature of the invention, the state of the prior art, the amount of guidance present in the specification, and the breadth of the claims, undue experimentation would be required to practice the claimed invention. The person of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention because the recited dosage does not relate to any experiments involving living animals. The skilled artisan, therefore, would be required to undertake excessive experimentation to determine an appropriate dosage regimen for a living patient.

Amended claims 7 and 8 are instantly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to compositions comprising the EEIIMD polypeptide and a fibrinolytic agent, and methods of using said composition. In some dependent claims, the agent is scuPA.

Claim 7 recites EEIIMD "in the range of 2μM to 10μM", which is confusing. Concentration is necessarily a relative term in which the amount of one component in a composition is compared to the amount of the whole. In this case, it is not clear to what concentration 2μM to 10μM refers, i.e. the concentration of the polypeptide in the composition to be administered, the concentration of the polypeptide in the subject's circulatory system following administration, or some other concentration. Clarification is required. Because claim 8 depends from indefinite claim 7 and does not clarify the point of confusion, it must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

Claims 1, 2, 7, and 8 stand rejected under 35 U.S.C. 103 as being obvious over U.S. '143 (cited in prior action) taken in light of Zhang et al. (cited in prior action). In the first Office action on the merits, the examiner asserted that combining EEIIMD and scUPA would have been obvious to the person of ordinary skill in the art, and that the skilled artisan would have been motivated to do so for the expected benefit of increasing the safety of treating thrombic disorders with plasminogen activators.

In response, applicants assert that because U.S. '143 does not teach co-administration of EEIIMD and scUPA, and Zhang et al. teaches away from the present invention, the person of ordinary skill in the art would have had no motivation to combine EEIIMD and scuPA. Applicants also assert that the examiner used improper hindsight reasoning to combine the teachings of U.S. '143 and Zhang et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. So long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, however, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, because EEIIMD and its parent protein, PAI-1, were known modulators of the fibrinolytic activities of tPA and uPA at the time the invention was made (see, for example, Zhang et al.), the person of ordinary skill in the art would have been motivated to combine EEIIMD and scuPA for the benefit of controlling the activity of scuPA *in vitro* or *in vivo*. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicant's arguments regarding method claims 7 and 8, the recitation of "enhancing the fibrinolytic activity of a fibrinolytic agent" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). These method claims comprise a single administration step of a composition, and said step does not necessitate that EEIIMD must enhance the fibrinolytic activity of the selected fibrinolytic agent, only that said agent must have some activity upon co-administration and that no cranial hemorrhage results from said co-administration.

The rejection of claims 1, 2, 7, and 8 under 35 U.S.C. § 103 is upheld.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

leb

SANDRA E. SAUCIER
PRIMARY EXAMINER